

# Food and food additives in severe atopic dermatitis

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In this study the role of food additives, tyramine and acetylsalicylic acid, was investigated by double-blind placebo-controlled challenges (DBPCC) in 25 children with severe atopic dermatitis (AD). All children challenged with foods ( $n = 24$ ), except one, showed one or more positive reactions to the DBPCC with foods. Positive reactions presented as different combinations of flares of skin symptoms, intestinal symptoms and respiratory symptoms. Seventeen children (70.8%) showed a positive challenge to egg, 12 to wheat (50%), eight to milk (33.3%) and eight to soya (33.3%). Six children underwent DBPCC with food additives, tyramine and acetylsalicylic acid. All were found to demonstrate positive skin and/or intestinal reactions to at least one of the food additives. Two children reacted to tartrazine, three to sodium benzoate, two to sodium glutamate, two to sodium metabisulfite, four to acetylsalicylic acid and one to tyramine. It is concluded that some foods, food additives, tyramine and acetylsalicylic acid, can cause positive DBPCC in children with severe AD.

*Key words:* atopic dermatitis; challenge; food additives.

*Accepted for publication 12 July 1989*

## CLINICAL ASPECTS

**In this study it was demonstrated, by double-blind placebo-controlled challenges, that foods and food additives are able to induce exacerbations of skin symptoms in children with severe atopic dermatitis. Therefore, the institution of an appropriate diet is of value in treating children with severe atopic dermatitis.**

Although atopic dermatitis (AD) is a common disorder in childhood there are still many questions as to its pathogenetic features. The role of foods as an exacerbating factor has been demonstrated by experimental data and clinical observation in some children with AD (1, 11). However, the diagnosis of food allergy remains difficult, since different foods can be responsible for exacerbating skin symptoms in one patient and since skin testing and determination of specific IgE against foods is frequently associated with false positive and false negative results (6). At the moment, the golden standard in diagnosing food allergy is the double-blind placebo-controlled challenge (DBPCC) (10).

The role of food additives is still a matter of debate since no controlled study has been performed showing that food additives can induce AD.

The aim of this study was to investigate the role of food and food additives, by DBPCC, in 25 children with severe AD. In a number of the subjects the results of DBPCC with food were compared with the results of prick tests and specific IgE determination.

## MATERIAL AND METHODS

Twenty five children fulfilling the criteria of Hanifin & Lobitz (5) for the diagnosis of AD were selected for this study. All children suf-

ferred from severe AD, persistent for several months and unresponsive to antihistamines, topical lubricating creams and topical steroids. In all children, a detailed history was obtained with special attention to food intake and possible related AD exacerbations. The eventual positivity of the history for aggravation of the disease by food was not considered in the selection of the patients. Virtually all patients had undergone various elimination diets without notable success and some had used systemic steroids to control cutaneous symptoms. In these children, systemic steroids were stopped for at least 1 month before entering the study. No patient had a convincing history of a major anaphylactic or anaphylactoid reaction. Informed consent was obtained for each subject. Details of the patients are shown in Table 1.

All children were hospitalized and received an elemental diet by nasogastric tube during 1 or 2 weeks, while their local treatment was continued. The children younger than 2 years received Alfare (Nestle), the others received Vivonex (Eaton). At the beginning of the study,

prick tests and determination of specific IgE were performed. In all children the AD lesions improved after having received the elemental diet for 1 to 2 weeks. The improvement was significant in that their skin was almost free from active eczema lesions.

After obvious clinical improvement was obtained and after having stopped antihistamines for 1 week the DBPCC were performed by administering the food, food additive, tyramine, acetylsalicylic acid or placebo (= elemental diet) into the nasogastric tube. To simplify, tyramine and acetylsalicylic acid will be included in the group of food additives in the further text, even though these two substances are not food additives. Nineteen children were challenged with food, five with food and with food additives and one child only with food additives. The foods used for challenge were : egg (15 g), milk (30 ml), soya (30 ml) and wheat (10 g). The food additives were : tartrazine (0.1 mg), sodium benzoate (100 mg), sodium glutamate (100 mg) sodium metabisulfite (10 mg), acetylsalicylic acid (100 mg) and tyra-

Table 1  
History and clinical findings in the 25 children

|                    |                                                    |       |
|--------------------|----------------------------------------------------|-------|
| Age:               | mean: 3.5 years<br>range: 5.0 months to 13.8 years |       |
| Sex distribution:  | 13 boys/12 girls                                   |       |
| Personal history:  | asthma:                                            | 7/25  |
|                    | rhinitis:                                          | 4/25  |
|                    | asthma and rhinitis:                               | 4/25  |
|                    | no respiratory disease:                            | 10/25 |
| Family history     | atopic dermatitis:                                 | 10/25 |
|                    | asthma:                                            | 9/25  |
|                    | rhinitis:                                          | 4/25  |
| Atopic dermatitis: |                                                    |       |
| -Age of onset:     | mean: 6.6 months<br>range: 2 weeks to 4 years      |       |
| -Characteristics:  | -xerosis:                                          | 25/25 |
|                    | -flexural involvement:                             | 25/25 |
|                    | -facial involvement:                               | 18/25 |
|                    | -trunk involvement:                                | 20/25 |
|                    | -scalp lesions:                                    | 9/25  |
|                    | -Dennie - Morgan infraorbital folds:               | 12/25 |

Table 2

Number of positive DBPCC with food and food additives

|                       |       |
|-----------------------|-------|
| Food:                 |       |
| milk                  | 8/24  |
| soya                  | 8/24  |
| egg                   | 17/24 |
| wheat                 | 12/24 |
| Food additives:       |       |
| tartrazine            | 2/6   |
| sodium benzoate       | 3/6   |
| sodium glutamate      | 2/6   |
| sodium metabisulfite  | 2/6   |
| acetyl salicylic acid | 4/6   |
| tyramine              | 1/6   |
| Placebo:              | 0/132 |

mine (20 mg). Two challenges were performed each day, one at 9 a.m. and one at 2 p.m. One of the daily challenges was, in a random order, always with placebo and the other with a single food or food additive. A dietician randomized all challenges so that nursing staff, patients, parents and investigators were unaware of the content of any given challenge. Before and hourly after each challenge the children were clinically scored for 4 h. If any symptoms secondary to the challenge were suspected, the challenge was interrupted and no second challenge was performed that same day. If there was any doubt concerning the appearance of symptoms, the challenge was repeated double-blind a few days later. Each challenge was started if all symptoms due to the prior challenge had resolved completely. In each patient the code was broken after having performed all challenges. After discharge from the hospital the children received a diet free from the foods or food additives evoking a positive DBPCC.

A standard sheet was used to score all challenges. Patients were scored for skin symptoms (redness, hives, swelling, itching), respiratory symptoms (runny nose, cough, wheezing, dyspnea) and intestinal symptoms (nausea, vomiting, diarrhea, abdominal pain). All reactions were scored for time of onset, severity (0-4 scale) and duration during the first 4 h after provocation.

Skin prick tests were performed with buffer solution (= negative control), histamine, codeine phosphate, egg and milk (Haarlem Allergen Laboratories, HAL, Brussels, Belgium). Wheal reactions 3 mm greater than the negative control were considered positive. Prick tests were performed on skin that was clinically free from AD.

Specific IgE (RAST, Pharmacia, Belgium) was determined against egg and milk.

## RESULTS

### *Double-blind placebo-controlled challenges*

**Food:** All children challenged with food ( $n = 24$ ), except one, reacted to one or more challenges with food (Table 2). One child reacted to the four foods, four children reacted to three foods while most reacted to one or two foods. Egg accounted for most of the positive challenges; 17/24 (70.8%) children showed a positive reaction to egg. There were no positive reactions to the challenges with placebo. Most reactions occurred within 15 min and all positive reactions occurred within 1 h. All reactions resolved within 4 h. There were no isolated late reactions observed although the patients were scored for 4 h. In some patients a biphasic course of cutaneous symptoms was suspected within 4 h.

A total of 96 food challenges were performed of which 45 (46.8%) were scored positive. Most reactions (23/45) were flares of isolated skin symptoms consisting of a diffuse erythematous macular or morbiliform rash and pruritus. Nausea, abdominal pain and diarrhea with or without skin symptoms or without respiratory complaints, including wheezing, severe nasal congestion or cough, isolated or in combination with other symptoms, were seen in 13 of the 45 positive reactions. One infant developed hypotension, severe wheezing and rash after provocation with egg, although the history of this infant did not implicate egg as a potential cause of AD. In this case, emergency treatment with epinephrine and steroids was instituted and symptoms disappeared within 1 h. Details of the symptoms induced by the food challenges are shown in Table 3.

*Food additives:* Challenge with food additives showed positive reactions with all food additives tested (Table 2). All the subjects challenged reacted positively to at least one food additive. Most reactions were exacerbations of isolated skin symptoms consisting of pruritus and redness of the skin. All positive reactions occurred within 10 min after administration of the food additive. No late reactions were seen. Only two intestinal reactions were observed: one child showed abdominal pain in association with rash after challenge with sodium benzoate and one child showed isolated abdominal pain with diarrhea after challenge with tyramine. There were no respiratory symptoms after challenge with food additives. No child reacted to the placebo.

#### *Relationship between history and results of the DBPCC*

Of the eight children demonstrating a positive DBPCC to milk, five had a history suggesting aggravation of AD after intake of milk, but three were unaware of any harm induced by milk. In the group of 16 children showing a negative DBPCC with milk, only two were suspected to react towards milk. It was found

that only 4/17 showing a positive DBPCC with egg, also had a positive history for egg. The seven children who demonstrated a negative DBPCC with egg, also had a negative history for that food.

None of the children had a positive history for wheat or soya, although all of them regularly ate bread, and most of them were encouraged to drink soya. A relationship between the results of the DBPCC and the ingestion of food additives could be obtained by history.

#### *Relationship between specific IgE and DBPCC*

In 22 patients specific IgE was determined to milk and in 23 patients to egg. There was no correlation between the results of the BDPCC and specific IgE determination for milk. There was no false positive IgE for egg, but false negative results were found in eight of the 23 patients (Table 4).

#### *Relationship between prick test and DBPCC*

Prick testing with milk showed false positive and false negative results. Prick testing with egg showed no false positive results. However, there were nine children with a negative prick test to egg in which the DBPCC was positive (Table 4).

Table 3

Symptoms induced by the food challenge.  
(Number of positive food challenge)

|             |                                                                                                                                 |
|-------------|---------------------------------------------------------------------------------------------------------------------------------|
| Milk (8):   | skin : (3)<br>skin + respiratory : (2)<br>skin + intestinal : (2)<br>skin + respiratory + intestinal : (1)                      |
| Soya (8):   | skin : (3)<br>skin + respiratory : (2)<br>skin + intestinal : (1)<br>skin + respiratory + intestinal : (1)<br>intestinal : (1)  |
| Egg (17):   | skin : (8)<br>skin + respiratory : (2)<br>skin + intestinal : (2)<br>skin + respiratory + intestinal : (3)<br>respiratory : (2) |
| Wheat (12): | skin : (9)<br>skin + respiratory : (3)                                                                                          |

#### *Follow-up*

After discharge from the hospital the children were followed up for a mean period of 10.6 months (range: 2 to 22 months) while they were encouraged to take a diet free from the substances to which they showed a positive DBPC. One child was lost from follow-up, leaving 24 children in whom appropriate follow-up data could be obtained. In 17/24 children (70.8%) there was marked improvement of AD. The remaining seven children reported no improvement. In only 3/24 children was the prescribed diet neglected while all the others were able to adhere strictly to the prescribed diet.

Table 4  
Relationship between DBPCC and specific IgE or skin test to milk and egg

|       | Milk               |     |                    |     | Egg                |     |                    |     |
|-------|--------------------|-----|--------------------|-----|--------------------|-----|--------------------|-----|
|       | spec. IgE (n = 22) |     | skin test (n = 15) |     | spec. IgE (n = 23) |     | skin test (n = 17) |     |
|       | Pos                | Neg | Pos                | Neg | Pos                | Neg | Pos                | Neg |
| DBPCC |                    |     |                    |     |                    |     |                    |     |
| Pos   | 2                  | 7   | 3                  | 2   | 9                  | 0   | 3                  | 0   |
| Neg   | 5                  | 8   | 4                  | 6   | 8                  | 6   | 9                  | 5   |

## DISCUSSION

In this selected group of children with severe AD it was demonstrated that food and food additives can frequently exacerbate skin symptoms. Since all challenges with foods and food additives were performed double-blind and since no subject reacted to the administration of placebo (a total of 132 placebo challenges), the significance of the obtained results is without question. However, this study was performed on a selected population with severe AD and the prevalence of intolerance to foods or food additives in AD remains unknown. In recent years, the role of food hypersensitivity in AD was demonstrated (1, 11). Most studies were performed on selected populations of children with severe disease. In the severe AD children challenged by Sampson & McCaskill, approximately 60% showed positive food reactions (10, 11). In a recent study by Burks et al. of children with mild to severe AD, it was found that 33% showed a positive reaction to the DBPCC (2). The authors conclude that food hypersensitivity appears to play a significant role in all degrees of skin involvement. In this study, it was also suggested that any child with AD, unresponsive to classical therapy with lubricating creams or ointments, topical corticosteroids, antihistamines, and antibiotics should be evaluated for food hypersensitivity by DBPCC. As in other reports, the relationship between history, specific IgE determination or prick testing and the results of the DBPCC is poor (2, 10, 11). However, in the present study no false positive prick tests nor specific IgE was found for egg. This finding suggests that when a patient has specific IgE to egg, or a positive prick

test to egg it can be assumed that the DBPCC with egg will be positive.

Presently, the proposed mechanism by which foods exacerbate AD symptoms is the late-phase IgE response. After an IgE-mediated reaction there is degranulation of mast cells, resulting in an immediate skin response (redness, urticaria) and a late skin response (cellular infiltration). A number of mast cell mediators, including neutrophil chemotactic factor of anaphylaxis (NCF-A) and inflammatory factors of anaphylaxis (IFA), are capable of recruiting both neutrophils and eosinophils into the skin. Once these cells have arrived, they are capable of releasing or generating additional mediators, resulting in an inflammatory reaction. This mechanism has been extensively studied in allergic asthma, but several findings suggest that this mechanism also applies for AD (9). The observed skin symptoms in our patients after DBPCC resemble the immediate skin response (= redness, pruritus and urticaria appearing with minutes of challenge). We found no manifestation of exacerbation of AD after the challenge, but this is probably due to the immediate withdrawal of the food from the diet. In the experimental late cutaneous response it was found that after ingestion of an allergen there was a progressive accumulation of eosinophils and neutrophils, which reached a maximum concentration at 6 to 8 h (8). After 24 to 48 h fibrin deposition and a mononuclear round-cell infiltrate of monocytes and lymphocytes was noted (4, 13). Biopsy findings of these lesions are indistinguishable from those of the skin of patients with AD (8). In a study by Leiferman et al. major basic protein (MBP), a cytolytic protein secreted almost exclusively by eosinophils, was detected in

the upper dermis of biopsy specimens taken from chronic AD lesions (7). MBP was not found in biopsy specimens from uninvolved skin sites in these same patients, indicating that this eosinophil product was the result of specific deposition and not of non-specific sequestration via the circulation. In another study by Sampson MBP was found in the skin lesions after DBPCC in two food-allergic patients (12). This finding supports the theory that food allergen-induced mast cell activation may trigger both an immediate and a late phase response in the skin. Furthermore, it seems that the mononuclear round cell infiltrate found in AD lesions may be the result of an IgE-mediated mechanism (12). Thus, all these observations suggest that AD is a late-phase cutaneous reaction, occurring after an initial mast cell degranulation. IgE-mediated mechanisms are responsible for the mast cell degranulation, but it seems reasonable to assume that this degranulation can also be evoked by non-allergic mechanisms, which could be demonstrated in bronchial asthma (9). Since in allergic asthma, the late phase reaction is accompanied by an increase in non-allergic bronchial hyperresponsiveness, dermal hyperresponsiveness could occur during AD. This could lead to exacerbations of AD symptoms after provocation with non-allergic triggers, creating the same vicious circle encountered in allergic asthma (9). This could explain why AD patients report exacerbations of their skin lesions after being exposed to allergens (food, inhalants) and to non-allergic stimuli (itching, stress, humidity).

To the best of our knowledge, the role of food additives in AD has not been studied. However, from several anecdotes the role of food additives has been suspected for a long time (i.e. exacerbation of AD after chocolate intake) and it has been estimated that ingestion of tartrazine or benzoic acid may exacerbate the skin lesions in at least 5% of all children with AD (3). By DBPCC in the present study, it was found that all subjects reacted to one or more food additives. Since these substances are extensively included in Western diets, it appears that the importance of food additives in AD has been largely neglected. In a study by Supramaniam et al.

et al. it was noted that DBPCC with food additives were positive in 42% of children suffering from urticaria and/or angio-edema (14). From this study it was also concluded that intolerance to food additives was not associated with atopy, suggesting that it is not an IgE-mediated phenomenon.

In our study, food additives caused pruritus and redness of the skin in most subjects tested. All reactions started within 10 min of the DBPCC, resembling an immediate mast cell degranulation. Since, in AD, mast cell degranulation is the initiating feature to the late phase reaction (i.e. cellular infiltration) it is suggested that food additives can aggravate AD, although this hypothesis needs to be proven.

It remains also unclear whether food additives aggravate AD by inducing erythema and urticaria, which seems to be the most likely explanation, or whether they are directly capable of worsening AD.

In conclusion, this study demonstrates that foods and food additives cause positive DBPCC in children with severe AD. Since the study was performed on a selected population of children with AD, further studies are needed to elucidate the prevalence of these phenomena in all degrees of childhood AD.

## ACKNOWLEDGEMENTS

We thank M. De Clercq, C. Schippers and A. M. Van De Sompel, the dieticians, for their cooperation in this study.

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